

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date
23 December 2004 (23.12.2004)

PCT

(10) International Publication Number
WO 2004/110415 A2

(51) International Patent Classification⁷: **A61K 31/00**

(21) International Application Number: PCT/EP2004/051048

(22) International Filing Date: 7 June 2004 (07.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: PCT/EP03/50220 10 June 2003 (10.06.2003) EP

(71) Applicant (for all designated States except US): JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): JANSSENS, Frans, Eduard [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2460 Beerse (BE). SOMMEN, François, Maria [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). DE BOECK, Benoît, Christian, Albert, Ghislain [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). LEENAERTS, Joseph, Elisabeth [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). VAN ROOSBROECK, Yves, Emiel, Maria [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). MEERT, Theo, Frans [BE/BE];

(74) Common Representative: JANSSEN PHARMACEUTICA N.V.; Turnhoutseweg 30, B-2340 Beerse (BE).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

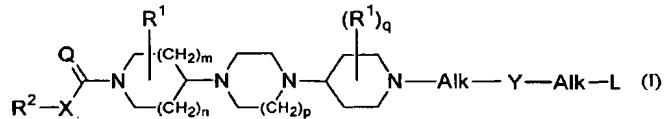
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

[Continued on next page]

(54) Title: NOVEL FORMULATIONS FOR OPIOID-BASED TREATMENTS OF PAIN COMPRISING SUBSTITUTED 1,4-DIPIPERIDIN-4-YL-PIPERAZINE DERIVATIVES



(57) Abstract: This invention concerns novel formulations for opioid-based treatments of pain and/or nociception comprising opioid analgesics and 1,4-di-piperidin-4-yl-piperazine derivatives having neurokinin antagonistic activity, in particular NK₁ antagonistic activity, the use of said formulation for the manufacture of a medicament for the prevention and/or treatment of emesis, pain and/or nociception, in particular in opioid-based acute and chronic pain treatments, more in particular in inflammatory, postoperative, emergency room (ER), breakthrough, neuropathic and cancer pain treatments and the use of an NK₁-receptor antagonist for the manufacture of a medicament for the prevention and/or treatment of respiratory depression in opioid-based treatments of pain. The pharmaceutical formulations according to the invention comprise a pharmaceutically acceptable carrier and, as active ingredients, a therapeutically effective amount of an opioid analgesic and NK₁-antagonists according to the general Formula (I) the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the N-oxide form thereof and prodrugs thereof, wherein all substituents are defined as in Claim 1. The pharmaceutical composition according to the invention reduces to a large extent a number of unwanted sideeffects associated with opioid analgesics, in particular emesis, respiratory depression and tolerance, thereby increasing the total tolerability of said opioids in pain treatment.

WO 2004/110415 A2



MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- of inventorship (Rule 4.17(iv)) for US only

Published:

- without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.